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ORIGINAL ARTICLE

Comparison of Clinical Versus Ultrasound-Determined Synovitis in Juvenile Idiopathic Arthritis

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Objective. **To compare clinical evaluation and ultrasonography (US) in the assessment of joint synovitis in children with juvenile idiopathic arthritis (JIA).**

Methods. **Thirty-two patients underwent clinical evaluation of 52 joints by 2 pediatric rheumatologists. Joints were assessed for swelling, tenderness/pain on motion, and restricted motion. The same joints were scanned independently by an experienced sonographer for synovial hyperplasia, joint effusion, and power Doppler (PD) signal.**

Results. **In total, 1,664 joints were assessed both clinically and with US. On clinical examination, 98 joints (5.9%) were swollen, 59 joints (3.5%) were tender, and 40 joints (2.4%) had restricted motion. On US evaluation, 125 joints (7.5%) had synovial hyperplasia, 153 joints (9.2%) had joint effusion, and 53 joints (3.2%) had PD signal. A total of 104 (6.3%) and 167 (10%) joints had clinical and US synovitis, respectively. Of the 1,560 clinically normal joints, 86 (5.5%) had subclinical synovitis (i.e., had synovitis on US). US led to classifying 5 patients as having polyarthritis who were classified as having oligoarthritis or were found to have no synovitis on clinical evaluation. US variables were moderately correlated with clinical measures of joint swelling, but poorly correlated with those of joint tenderness/pain on motion and restricted motion. Overall, correlations were lower for PD signal than for synovial hyperplasia and joint effusion.**

Conclusion. **We found that subclinical synovitis as detected by US is common in children with JIA. This finding may have important implications for patient classification and may affect the choice of the optimal therapeutic strategy in individual patients.**

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease that affects ~1 of every 1,000 children worldwide (1). Joint inflammation has a central role in the development of cartilage damage and bony erosion. Although a number of measures are applied in the evaluation of disease activity in JIA (2), therapeutic decisions are primarily influenced by the presence of synovitis on clinical examination. However, studies of adult patients with rheumatoid arthritis (RA) and of children with JIA have shown that current techniques of clinical examination may underestimate significant joint inflammation (3–5). Furthermore, histologic evidence of synovial inflammation has been found in asymptomatic joints (6). Underrecognition of synovitis may lead to delayed diagnosis and treatment of joint disease or suboptimal suppression of joint inflammation with antirheumatic therapy.

The issue of subclinical synovitis may be particularly relevant in JIA. In the current International League of Associations for Rheumatology (ILAR) classification, children with JIA are defined as having oligoarthritis or polyarthritis on the basis of the number of affected joints (≤4 or >4, respectively) (7). Furthermore, the presence of active disease in a minimum of 5 joints is a prerequisite for patient inclusion in clinical trials of second-line or biologic agents (8–13). Therefore, the presence of subclinical disease in some joints may alter patient classification or affect the identification of patients requiring more aggressive treatment. A recent study has shown that a sizable proportion of adult patients who had oligoarthritis clini-

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cally could be reclassified as having a polyarticular disease by ultrasonography (US) (5).

US is increasingly used by clinicians for the evaluation of joint disease. It has been shown to be sensitive in the detection of synovitis and bone erosion in both small and large joints (14,15). US has several advantages over other imaging methods, including noninvasiveness, rapidity of performance, relatively low cost, ability to scan multiple joints at one time, repeatability, safety, and high patient acceptability. Another advantage of US is that it is the only imaging technique that can be coupled with the conventional clinical approach to the patient in the standard rheumatology setting. Implementation of US in adult rheumatology clinical practice has been reported to have a significant effect on clinical decision making (16).

The purposes of the present study were to compare clinical evaluation and US in the assessment of synovitis and to determine the prevalence of subclinical synovitis defined by US in children with JIA.

PATIENTS AND METHODS

Patient selection. All consecutive patients who met the ILAR criteria for JIA (7), attended the rheumatology outpatient clinic of the Department of Pediatrics of the Fondazione IRCSS Policlinico San Matteo, Pavia, Italy between January and April 2008, and were seen the day when the ultrasonographer was available (generally once a week) were included in the study. Informed consent was obtained from all patients, parents, or guardians, as appropriate. The study protocol was approved by the Institutional Review Board of the Fondazione Istituto Ricerca Cura Carattere Scientifico Policlinico S. Matteo of Pavia, Italy.

Clinical and laboratory assessment. The following data were recorded for each patient at study visit: sex, age at onset, ILAR category, and disease duration. Clinical evaluation was performed by 2 pediatric rheumatologists (SM-M and CV) who had 8 and 2 years of clinical rheumatology practice, respectively, and who were blinded to US findings and reached consensus on the presence and grading of articular indices in each joint. A total of 52 joints (2 elbows, 2 wrists, 10 metacarpophalangeal [MCP] joints, 10 proximal interphalangeal [PIP] joints, 2 knees, 2 ankles, 2 subtalar joints, 2 tarsal joints, 10 metatarsophalangeal [MTP] joints, and 10 foot interphalangeal [IP] joints) were assessed for swelling, tenderness/pain on motion, and restricted motion according to a standard technique (2). The shoulder and hip joints were not included because clinical detection of synovitis in these joints is difficult (17,18). Temporomandibular joints were not included because US has been found to have low sensitivity for the detection of arthritis changes in JIA (19). Each articular index was scored as present or absent and, if present, was graded semiquantitatively from 1 to 3 (where 1 = mild, 2 = moderate, and 3 = severe), as previously described (2). A joint with clinical synovitis was defined as a joint with active disease, defined as the presence of swelling or, if no swelling was present, of tenderness/pain on motion and restricted motion (2,20).

The pediatric rheumatologists also rated the overall disease activity on a 10-cm visual analog scale (VAS; where 0 = no activity and 10 = maximum activity). A parent was asked to rate a child's overall well-being on a 10-cm VAS (where 0 = very good and 10 = very poor) and the intensity of a child's pain on a 10-cm VAS (where 0 = no pain and 10 = maximum pain). The parent was also asked to assess a child's functional ability by completing the Italian version of the Juvenile Arthritis Functionality Scale (JAFS) (21). Briefly, the JAFS is a 15-item questionnaire in which the ability of the child to perform each task is scored as follows: 0 = without difficulty, 1 = with difficulty, and 2 = unable to do. The total score ranges from 0 to 30. Laboratory assessment included determination of erythrocyte sedimentation rate (ESR) and C-reactive protein level.

Based on articular assessment, the following clinical measures were computed: count of joints with swelling, tenderness/pain on motion, restricted motion, and active disease; swelling, pain/tenderness, and restricted motion scores (calculated as the sum of the severity ratings obtained in each joint); and overall articular severity score (calculated as the sum of the swelling, pain/tenderness, and restricted motion scores). The overall level of JIA activity was estimated by calculating the Juvenile Arthritis Disease Activity Score (JADAS) (22). Briefly, the JADAS is obtained by summing the scores of 4 measures: 1) physician's global assessment, 2) parent's global assessment, 3) active joint count, and 4) ESR (normalized to a 0–10 range). The score of the 52-joint JADAS (JADAS52) used in this study ranges from 0 to 82.

Ultrasonographic evaluation. US assessment was performed separately, immediately after clinical evaluation, by an experienced rheumatologist (OE) with more than 9 years of experience in musculoskeletal US. The US examiner was blinded to clinical findings. The same 52 joints assessed in the clinical evaluation were scanned for the presence of synovial hyperplasia, joint effusion, and power Doppler (PD) signal. US examination was performed with Logiq 9 (General Electric Medical Systems, Milwaukee, WI), equipped with an 8–15-MHz volumetric probe (4D16L) and linear probe (9L).

Synovial hyperplasia was defined as an abnormally hypoechoic joint space, distinct from the intraarticular fat pad and noncompressible with the transducer. Joint effusion was detected as the presence of an abnormally anechoic space within the joint that was compressible. PD signal was considered positive in the presence of vessel dots on PD images. In each joint, synovial hyperplasia and joint effusion were graded as follows: 0 = absent, 1 = mild, 2 = moderate, and 3 = marked. PD signal was graded as follows: 0 = absent, 1 = presence of single/vessel dots, 2 = presence of confluent vessel dots in less than half of the synovial area, and 3 = presence of confluent vessel dots in more than half of the synovial area. An example of the US grading system is shown in Figure 1. All of the US findings were interpreted using both longitudinal and transverse planes. A US count of joints with synovial hyperplasia,

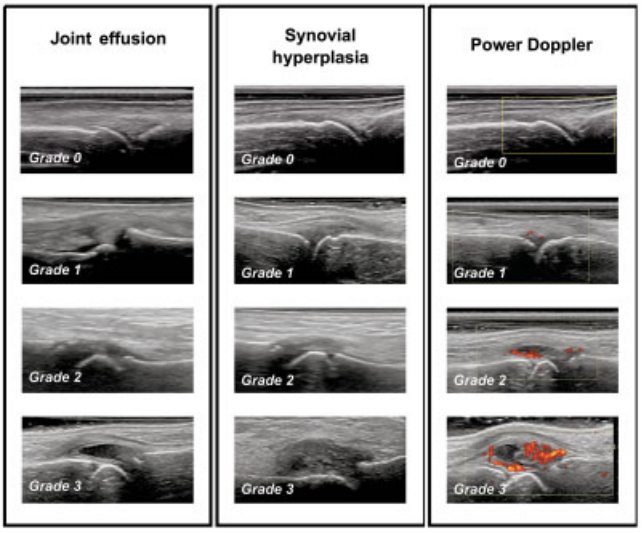

Figure 1. Grading of ultrasound parameters.

joint effusion, and PD signal (each ranging from 0 to 52), and a US score for synovial hyperplasia, joint effusion, and PD signal (calculated as the sum of severity rating obtained in each joint, each ranging from 0 to 156) were computed in each patient. A joint with US synovitis was defined as a joint in which any of the 3 US abnormalities was detectable. All of the joints were also assessed for the presence of tenosynovitis, defined as the presence of hypoechoic or anechoic thickened tissue with or without fluid within the tendon sheath that was seen in 2 perpendicular planes and that could exhibit PD signal. However, tenosynovitis was not incorporated in the definition of US synovitis because clinicians were not asked to specifically assess this feature. The US examination technique as well as the definitions and scoring of US features were based on published guidelines or descriptions, particularly those provided by the Outcome Measures in Rheumatology Clinical Trials (23–26).

Interobserver reproducibility of US was determined by comparing the findings of 2 ultrasonographers, who independently scanned on the same day 195 joints in a random subset of 15 patients. Intraobserver reproducibility was calculated using stored images of the same patient subgroup 3 months after the end of the study.

Statistical analysis. Descriptive statistics were reported as means, SDs, medians, and interquartile ranges (IQRs) for continuous variables, and as absolute frequencies and percentages for categorical variables. Correlations between clinical and US parameters were calculated using Spearman's rank statistics. Correlations were considered to be high, moderate, or poor when they were >0.7, $0.4–0.7$, or <0.4, respectively (27). Given the descriptive nature of the study, which only explores the strength of the associations, no adjustment for multiple test bias or intrapatient correlation was performed. However, we did a sensitivity analysis to investigate, in a marginal logistic model, the association of positive findings obtained with clinical or US evaluation, while controlling for the joints examined and accounting for intrapatient correlation (through calculation of sandwich-Huber-White robust standard errors). This analysis confirmed the results (data not shown). The level of agreement between the presence of each clinical and US feature was estimated with the unweighted kappa statistics (28,29). Interobserver and intraobserver reproducibility was assessed by computing the percentage of exact agreement and by means of the kappa statistics (unweighted for dichotomous scoring and weighted for semiquantitative scoring). Agreement for semiquantitative scoring was also assessed by calculating the intraclass correlation coefficient (ICC) (30). The level of kappa agreement was defined as follows: ≤ 0.20 = poor, 0.21–0.40 = fair, 0.41–0.60 = moderate, 0.61–0.80 = good, and 0.81–1.00 = almost perfect (31). ICC values were classified as follows: <0.4 = poor agreement, ≥ 0.4 to <0.75 = moderate agreement, and ≥ 0.75 = good agreement (32). The statistical package used was Stata, version 10 (StataCorp, College Station, TX).

RESULTS

Patient characteristics. A total of 32 patients, 5 boys and 27 girls, were included in the study. Eight patients had persistent oligoarthritis, 12 had extended oligoarthritis, 7 had rheumatoid factor–negative polyarthritis, 1 had psoriatic arthritis, and 4 had enthesitis-related arthritis. The median age at disease onset was 4.1 years (IQR 2–8.4 years) and the median disease duration was 3.7 years (IQR 2.1–8.2 years). Values of clinical and laboratory indicators of JIA activity and results of the US assessment are shown in Table 1. The study patients had, on average, a low level of disease activity.

Clinical findings. In total, 1,664 joints were assessed both clinically and with US (Table 2). On clinical examination, 98 joints (5.9%) were swollen, 59 joints (3.5%) were tender, 40 joints (2.4%) had restricted motion, and 104 joints (6.3%) had active disease (i.e., had clinical synovitis). Among the 104 joints with clinical synovitis, the most frequently affected were the knees (33.7%), followed by the MCP joints (13.5%), PIP joints (12.5%), ankles (11.5%), and wrists (9.6%). Of the 28 patients who had clinical synovitis, 10 (35.7%) had involvement of only 1 joint (monarthritis), 10 (35.7%) had involvement of 2–4 joints (oligoarthritis), and 8 (28.6%) had involvement of 5 or more joints (Figure 2).

US findings. On US evaluation, 125 joints (7.5%) had synovial hyperplasia, 153 joints (9.2%) had joint effusion, and 53 joints (3.2%) had PD signal (Table 2). A total of 167 joints (10.0%) had US synovitis (i.e., had 1 or more of the 3 US abnormalities). US abnormalities were seen most frequently in the knees, followed by the wrists, MCP joints, PIP joints, ankles, and MTP joints. A distinctive high frequency of PD signal was seen in the wrists, which accounted for 24.5% of the 53 joints with this US abnormality. Of the 30 joints (1.8%) with US tenosynovitis, 9 (30%) were ankles or subtalar joints. Of the 31 patients with US synovitis, 8 (25.8%) had involvement of only 1

Table 1. Values of clinical and laboratory indicators of disease activity and US findings in the 32 study patients*

	Score range	Mean ± SD	Median (IQR)
Clinical features			
Physician's global assessment	0–10	4.0 ± 4.0	1.8 (0.5–8.5)
Parent's global assessment	0–10	2.3 ± 2.9	1.0 (0–3.0)
Parent's pain assessment	0–10	2.1 ± 2.8	1.0 (0–3.0)
Swollen joint count	0–52	3.3 ± 4.5	2 (1–3.5)
Tender/painful joint count	0–52	1.8 ± 3.0	1 (0–2)
Restricted joint count	0–52	1.3 ± 2.1	1 (0–1.5)
Active joint count	0–52	3.5 ± 4.6	2 (1–4)
Swelling score	0–156	3.8 ± 5.1	2 (1–4)
Tenderness/pain on motion score	0–156	2.2 ± 3.5	1 (0–2)
Restricted motion score	0–156	1.4 ± 2.1	1 (0–2)
Overall articular severity score	0–468	13.3 ± 16.4	8.5 (4.0–17.5)
JADAS52	0–82	8.2 ± 9.6	4.8 (2.0–10.8)
JAFS score	0–30	1.2 ± 2.03	0.0 (0.0–2.0)
ESR, mm/hour	0–140	18 ± 10	17 (12–21)
C-reactive protein level, mg/dl	0–∞	0.5 ± 0.8	1.8 (0.5–8.5)
US features			
Count of joints with synovial hyperplasia	0–52	3.9 ± 4.4	2 (1–4)
Count of joints with joint effusion	0–52	4.7 ± 5.0	3.5 (1–6)
Count of joints with power Doppler signal	0–52	1.7 ± 3.1	1.0 (0–2)
Synovial hyperplasia score	0–156	5.3 ± 7.0	2 (1–7.5)
Joint effusion score	0–156	5.4 ± 5.8	4 (1.5–7)
Power Doppler signal score	0–156	2.6 ± 4.9	2 (0–3)
Overall US severity score	0–468	13.3 ± 16.4	8.5 (4–17.5)
Count of joints with tenosynovitis	0–52	0.9 ± 2.3	0 (0–1)

* US = ultrasound; IQR = interquartile range; JADAS52 = 52-joint Juvenile Arthritis Disease Activity Score; JAFS = Juvenile Arthritis Functionality Scale; ESR = erythrocyte sedimentation rate.

joint (monarthritis), 9 (29%) had involvement of 2–4 joints (oligoarthritis), and 14 (45.2%) had involvement of 5 or more joints (polyarthritis). US led to classifying 5 patients as having polyarthritis who were classified as having oligoarthritis or who had no synovitis on clinical evaluation (Figure 2).

US synovitis in symptomatic or asymptomatic joints. US documented synovitis in 81 (77.9%) of 104 clinically synovitic joints. Overall, 1,560 (93.8%) of the 1,664 joints scanned were clinically asymptomatic. Of the 1,560 clinically normal joints, 86 (5.5%) had evidence of subclinical synovitis, i.e., had synovitis on US (19 PIP, 15 MTP, 12 wrist, 9 foot IP, 8 knee, 7 subtalar, 6 ankle, 5 intertarsal, 3 elbows, and 2 MCP joints). Clinical examination detected synovitis in 24 (1.6%) of 1,497 joints that were recorded as normal on US (7 PIP, 5 ankle, 3 foot IP, 2 knee, 2 wrist, 2 MTP, 2 subtalar, and 1 elbow joint).

The percentages of patients who had or did not have clinical or US synovitis in specific joints are depicted in

Table 2. Frequency of clinical and US features in specific joints*

	Clinical features				US features				
Joint	Swelling (n = 98)	TEN/POM (n = 59)	Restricted motion (n = 40)	Clinical synovitis (n = 104)	Synovial hyperplasia (n = 125)	Joint effusion (n = 153)	PD signal (n = 53)	US synovitis (n = 167)	Tenosynovitis (n = 30)
Elbow	2 (2.0)	4 (6.8)	1 (2.5)	2 (1.9)	2 (1.6)	4 (2.6)	0 (0)	4 (2.4)	0 (0)
Wrist	7 (7.1)	9 (15.3)	7 (17.5)	10 (9.6)	19 (15.2)	15 (9.8)	13 (24.5)	20 (12.0)	3 (10)
MCP	13 (13.3)	12 (20.3)	11 (27.5)	14 (13.5)	16 (12.8)	15 (9.8)	9 (17.0)	16 (9.6)	6 (20)
PIP	13 (13.3)	3 (5.1)	4 (10.0)	13 (12.5)	13 (10.4)	24 (15.7)	6 (11.3)	25 (15.0)	6 (20)
Knee	34 (34.7)	12 (20.3)	12 (30.0)	35 (33.7)	34 (27.2)	38 (24.8)	9 (17.0)	41 (24.6)	1 (3.3)
Ankle	12 (12.2)	7 (11.9)	3 (7.5)	12 (11.5)	10 (8.0)	12 (7.8)	6 (11.3)	13 (7.8)	4 (13.3)
Subtalar	2 (2.0)	2 (3.4)	1 (2.5)	3 (2.9)	4 (3.2)	9 (5.9)	2 (3.8)	9 (5.4)	5 (16.7)
Intertarsal	2 (2.0)	2 (3.4)	0 (0)	2 (1.9)	5 (4.0)	7 (4.6)	3 (5.7)	7 (4.5)	0 (0)
MTP	6 (6.1)	5 (8.5)	0 (0)	6 (5.8)	15 (12.0)	16 (10.5)	3 (5.7)	19 (11.4)	1 (3.3)
Foot IP	7 (7.1)	3 (5.1)	1 (2.5)	7 (6.7)	7 (5.6)	13 (8.5)	2 (3.8)	13 (7.8)	4 (13.3)

* Values are the number (percentage). US = ultrasound; TEN/POM = tenderness/pain on motion; PD = power Doppler; MCP = metacarpophalangeal; PIP = proximal interphalangeal; MTP = metatarsophalangeal; IP = interphalangeal.

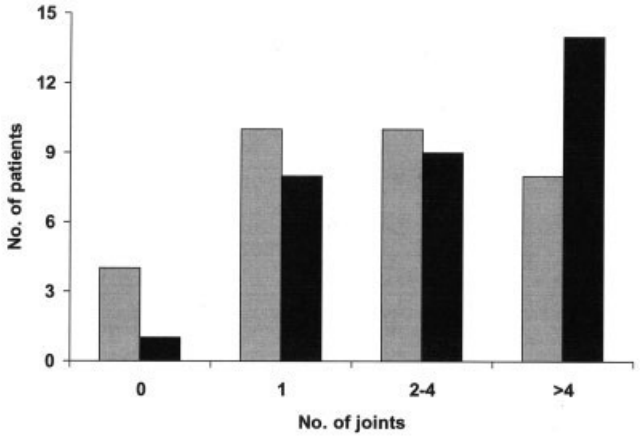

Figure 2. Number of patients with lack of synovitis, monarthritis, oligoarthritis, and polyarthritis as detected by clinical or ultrasound (US) examination in the 32 study patients. Shaded bars show the clinical assessment; solid bars show the US assessment.

Figure 3. The knee was the joint with a greater frequency of concordance between clinical and US evaluation. A relatively higher percentage of patients with US synovitis in clinically asymptomatic joints was seen for wrist, PIP, subtalar, intertarsal, MTP, and foot IP joints. The sole joint for which there was a greater frequency of clinical synovitis with a negative US assessment than of subclinical synovitis was the ankle.

Agreement between clinical and US examination. The kappa values for agreement between clinical and US examination were moderate for swelling versus synovial hyperplasia (0.46) and joint effusion (0.48), and fair for swelling versus PD signal (0.30) and for pain on motion/tenderness versus synovial hyperplasia (0.35), joint effusion (0.32), and PD signal (0.37).

Correlation between clinical and US parameters. Table 3 shows the Spearman's correlations between clinical and US parameters. Correlations between subjective physician's and parent's ratings, tender and restricted joint counts, tenderness and restricted motion scores, JADAS52, JAFS, and acute-phase reactants and US parameters were all poor. Among clinical parameters, swelling yielded moderate to strong correlations with US parameters, whereas correlations for tenderness/pain on motion and restricted motion were poor. Among US parameters, synovial hyperplasia and joint effusion yielded greater correlations with clinical variables than did PD signal. Age and disease duration did not affect the correlation between clinical and US findings (data not shown).

Interobserver and intraobserver reproducibility of US. Interobserver reproducibility assessment showed frequencies of exact agreement of 83%, 84%, and 95% for the presence/absence of joint effusion, synovial hypertrophy, and PD signal, respectively. The corresponding kappa values were 0.79, 0.70, and 0.89, respectively. The frequencies of exact agreement for the semiquantitative grading system were 60%, 64%, and 89% for the presence/absence of joint effusion, synovial hypertrophy, and PD signal, respectively. The corresponding weighted kappas and ICC values were 0.63, 0.68, and 0.85, respectively, and 0.82, 0.82, and 0.92, respectively.

Intraobserver reproducibility assessment showed frequencies of exact agreement of 90%, 91%, and 98% for the presence/absence of joint effusion, synovial hypertrophy, and PD signal, respectively. The frequencies of exact agreement for the semiquantitative grading system were 85%, 83%, and 96% for the presence/absence of joint effusion, synovial hypertrophy, and PD signal, respectively. The corresponding weighted kappas and ICC values were 0.86, 0.84, and 0.93, respectively, and 0.92, 0.91, and 0.96, respectively.

DISCUSSION

US is ideally suited for multiple joint assessment. It has been suggested that its routine use allows a marked improvement of a clinician's capability to detect both early and hidden features of synovitis (14). Previous studies

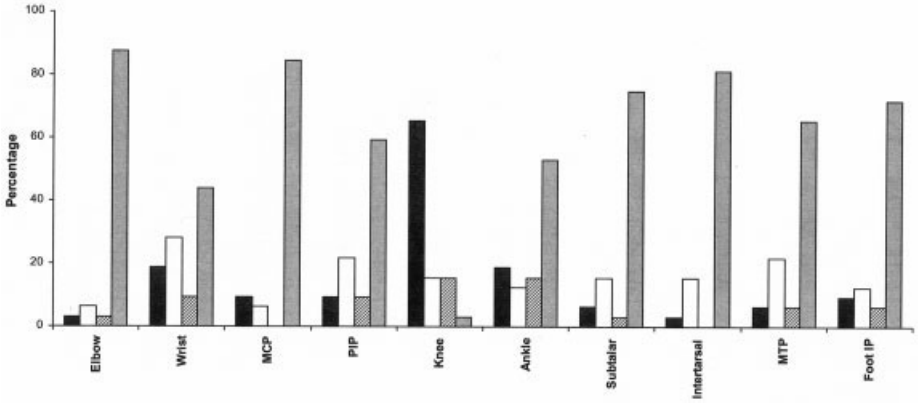

Figure 3. Percentages of patients with or without clinical or ultrasound (US) synovitis in specific joints. Solid bars show clinical synovitis and US synovitis; open bars show clinically asymptomatic and US synovitis; stippled bars show clinical synovitis and negative US; shaded bars show clinically asymptomatic and negative US. MCP = metacarpophalangeal; PIP = proximal interphalangeal; MTP = metatarsophalangeal; IP = interphalangeal.

Table 3. Spearman's correlations between clinical and ultrasonographic features*

Clinical features	US features						
	Count of joints with SH	Count of joints with JE	Count of joints with PDS	SH score	JE score	PDS score	Overall US severity score
Physician's global assessment	0.11	0.18	0.20	0.14	0.18	0.29	0.21
Parent's global assessment	−0.11	−0.17	−0.06	−0.04	−0.19	0.07	−0.06
Parent's pain assessment	−0.12	−0.17	−0.12	−0.09	−0.18	−0.07	−0.11
Swollen joint count	0.63†	0.69†	0.41†	0.63†	0.68†	0.42†	0.66†
Tender/painful joint count	0.19	0.26	0.20	0.24	0.24	0.29	0.30
Restricted joint count	0.30	0.28	0.01	0.36	0.27	0.14	0.31
Active joint count	0.60†	0.70‡	0.42†	0.60†	0.68†	0.43†	0.66†
Swelling score	0.60†	0.64†	0.46†	0.63†	0.66†	0.50†	0.67†
Tenderness/pain on motion score	0.15	0.20	0.17	0.19	0.19	0.24	0.25
Restricted motion score	0.21	0.19	−0.06	0.26	0.17	0.06	0.21
Overall articular severity score	0.41†	0.44†	0.30	0.45†	0.45†	0.37	0.48†
JADAS52	0.25	0.21	0.18	0.31	0.20	0.24	0.27
JAFS score	0.30	0.25	0.04	0.38	0.23	0.13	0.31
ESR	0.09	0.10	0.14	0.17	0.12	0.22	0.18
C-reactive protein level	0.10	−0.02	0.10	0.18	0.03	0.10	0.10

* US = ultrasound; SH = synovial hyperplasia; JE = joint effusion; PDS = power Doppler signal; JADAS52 = 52-joint Juvenile Arthritis Disease Activity Score; JAFS = Juvenile Arthritis Functionality Scale; ESR = erythrocyte sedimentation rate.
† Moderate correlation ($r \geq 0.4$ and ≤ 0.7).
‡ High correlation ($r > 0.7$).

have demonstrated the poor reliability of clinical examination of joints in children with JIA (33). It is, therefore, important to investigate the correlation between clinical and US assessment of joint synovitis and to establish whether US may improve the accuracy of detection of joint inflammation in children with JIA.

To our knowledge, our study is the first to compare clinical and US examination of multiple joints in children with JIA. We found that US detected more synovitis than clinical examination. Of the 1,667 scanned joints, 104 (6.3%) had clinical synovitis and 167 (10.0%) had US synovitis. Furthermore, 86 (51.5%) of the 167 joints that had US-documented synovitis were clinically normal (i.e., had subclinical synovitis). Subclinical synovitis was more common in small hand and wrist joints. This suggests that in these joints, US is helpful in identifying subtle inflammatory changes that may be overlooked by clinical assessment. Notably, discrepancies between pediatric rheumatologists in clinical examination of joints in children with JIA were found to be larger in small hand joints (33).

An unexpected finding was that clinical examination detected synovitis in 23 joints that were recorded as normal on US examination. This type of discordance was seen most commonly in the PIP and ankle joints. Disagreement in the PIP joints may be partially due to the abovementioned low reliability of clinical assessment of synovitis in small hand joints. The detection of clinical synovitis without evidence of US synovitis in the ankle joints may be explained by the frequent presence of tenosynovitis. Tendon sheath inflammation was assessed ultrasonographically, but was not incorporated in the definition of US synovitis. Because the clinicians were not asked to discriminate whether joint swelling was due to synovitis or tenosynovitis, it is likely that some ankle joints that were found to have synovitis clinically, but not on US, had tenosynovitis and not joint synovitis. The ankles were the majority (26.9%) of the joints that displayed tenosynovitis on US. Furthermore, they were the sole joints in which the frequency of clinical synovitis with a negative US was greater than that of subclinical synovitis. Recently, Burns et al (34) found that only 29% of 49 clinically swollen ankles in 34 children with JIA had tibiotalar effusion alone on US assessment, 69% of ankles had tenosynovitis and 39% had tenosynovitis alone, and 33% of ankles had both tenosynovitis and a tibiotalar effusion. The authors suggested that in JIA there is a clinical overdiagnosis of tibiotalar synovitis and an underdiagnosis of tendon involvement.

The findings in our study have important implications for the classification of JIA. Currently, the number of joints affected over time is adopted as a criterion to classify patients in presumably homogeneous categories (7). Patients are defined as having oligoarthritis or polyarthritis if they have 4 or fewer or 5 or more joints involved, respectively, during the first 6 months of disease. We found that US led us to classify as having polyarthritis 5 patients who were labeled as having oligoarthritis or were found to have no synovitis on clinical evaluation. In a recent study in JIA, 36% of clinically normal knees had evidence of effusion on US (35). Altogether, these findings suggest that US is more accurate than clinical assessment and may lead to reclassifying many patients with JIA. Furthermore, they add to the criticisms about the use of the number of affected joints as a classification parameter in JIA (36).

The presence of active disease in a minimum of 5 joints is a prerequisite for patient inclusion in most trials of second-line or biologic agents (8–13). By analogy, the same criterion is often used in standard clinical practice for prescribing the same medications. By detecting synovitis in clinically unaffected joints, US may increase the

number of patients who are candidates to receive such treatments. Another important issue that may be affected by US application is the assessment of clinical remission. The absence of joints with active arthritis, defined on clinical grounds, is a fundamental component of recently developed criteria for inactive disease in JIA (37). However, the present analysis and previous studies in adult patients with oligoarthritis (5) have shown a high prevalence of subclinical synovitis defined by US. It has been suggested that synovitis undetected clinically (but detectable by US) may be responsible for continuing the structural deterioration in patients with RA in clinical remission (38,39). Validation of clinical remission by US would, therefore, be important to make sure that it is coupled with biologic (i.e., true) remission and that it translates into lesser joint damage.

US findings were not correlated with subjective physicians' and parents' ratings, functional assessment, and acute-phase reactants. This is not surprising because these measures assess disease constructs that are only partially related to joint inflammation. US variables were moderately correlated with clinical measures of joint swelling, but poorly correlated with those of joint tenderness/pain on motion and restricted motion. Spearman's correlations were paralleled by the assessment of kappa agreement. These findings underscore the fact that swelling is the most reliable clinical indicator of joint synovitis in JIA. Overall, correlations and the level of kappa agreement between US findings and clinical parameters were lower for PD signal than for synovial hyperplasia and joint effusion. The lower correlations observed for PD signal may depend on the lower prevalence of this US feature as compared with that of synovial hyperplasia and joint effusion. PD technique detects synovial flow, which is a sign of increased synovial vascularization (40). In adult patients with RA, vascularization detected by PD has been found to predict radiographic progression (25,41). It remains to be established whether the relatively low prevalence of PD signal in our patients depends on the low severity of their arthritis or reflects a distinctive characteristic of the synovial process in JIA. Importantly, however, PD signal was distinctly more common in the wrist joint, which has been found to be the most vulnerable site of radiographic changes in JIA (42).

Some limitations of our study should be mentioned. The relationship between clinical and US findings was evaluated in a cross-sectional assessment. Therefore, we could not investigate the predictive value of US in relation to the efficacy of therapeutic interventions or course of joint disease over time. We did not validate the additional synovitis by other imaging techniques, such as magnetic resonance imaging. However, this technique is limited by its inability to scan more than one joint. Furthermore, general anesthesia is required in younger children. A healthy control group, which would have strengthened the study, was not available. We should emphasize that our results do not mean that US is an alternative to clinical examination. It should be regarded as a tool that complements conventional clinical examination. It should be acknowledged that joints not assessed in the study may be very important for individual patients and should be evaluated periodically as part of clinical care. For instance, shoulder, hip, and temporomandibular joints are involved in a sizable proportion of patients with JIA and are an important source of long-term damage (43,44). Exclusion of assessment of these joints and of tenosynovitis weakens the study results.

In summary, we found that subclinical synovitis as detected by US is common in children with JIA. This finding may have important implications for patient classification and for the selection of patients who are candidates to receive second-line or biologic medications. Furthermore, it may affect the definition of disease remission. Longitudinal assessments are, however, required to determine the true significance of subclinical disease. In the clinical setting, US appears particularly useful to define the relative role of tenosynovitis and synovial effusion/hyperplasia in the generation of joint swelling, particularly in the ankle joint.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Magni-Manzoni had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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